IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

SCHNEIDER et al. Atty. Ref: 1201-71

Serial No. to be assigned Art Unit: to be assigned

Filed: March 12, 1999 Examiner: to be assigned

For: **ULTRASOUND CONTRAST AGENTS AND METHODS OF MAKING AND USING THEM**

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March 12, 1999

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

REQUEST FOR INTERFERENCE
WITH PATENT UNDER 37 C.F.R. § 1.607

Applicants seek to have an interference declared between this application and two United States patents, U.S. Patent Nos. 5,573,751 and 5,409,688, and thus comply with 37 C.F.R. § 1.607, "Request By Applicant For Interference With Patent," as follows:

1. Identification Of Patent Under 37 C.F.R. § 1.607(a)(1)

Applicants seek an interference between this application and two United States Patents issued to Quay; (1) U.S. Patent No. 5,573,751 and its reexamination certificate (the "'751 patent"), and (2) U.S. Patent No. 5,409,688 (the "'688 patent"). The Code of Federal Regulations expressly permits declaration of an interference involving an application and more than one issued patent:

> An interference may be declared between one or more pending applications and one or more unexpired patents naming different inventors when, in the opinion of an examiner, any application and any unexpired patent contain claims for the same patentable invention.

37 C.F.R. § 1.601(i). Applicants believe inclusion of both Quay patents in the interference is necessary and proper. As an initial matter, Quay filed a terminal disclaimer without traverse in the '751 patent in response to an obviousness double patenting rejection over the '688 patent, effectively admitting that the patents are directed to the same subject matter. Moreover, as explained in more detail below, (1) certain of the Quay '751 patent claims encompass the same patentable invention as Applicants' claims, and (2) the "free gas microbubble" claims in the '751 and '688 patents encompass Applicants' claimed subject matter if Quay's current broad construction of this phrase is adopted. Thus, Applicants contend that a single interference involving the instant application and both Quay patents is both necessary and proper.

The Quay '751 patent was filed on December 21, 1994 and issued on November 12, 1996. A Reexamination Certificate (the "Certificate") confirming original claims 2, 3, 5, 6, 9 and 10, and amended claims 7, 11, 13-16 and 18-22 (referred to as "the '751 patent claims" herein) issued on March 9, 1999 and is attached as Exhibit 1. The Quay '688 patent was filed on June 5, 1992 and issued on April 25, 1995.

Applicants believe that both the Examiner of the related patent reexamination procedure concerning U.S. Patent No. 5,558,094 (the "'094 patent") and Administrative Patent Judge Sofocleus have suggested pursuing this interference. During reexamination of the '094 patent (and possibly the '751 patent, although those documents are not yet publicly available), the Examiner found that the confirmed '094 patent claims may interfere with application or patents involved in interference proceedings currently pending in the Patent and Trademark Office and acknowledged that the parties to those proceedings could seek to include the Quay patent in those proceedings. Applicants believe that this statement is a reference to Interference Nos. 103,880 and 103,881 which involve a patent and application owned by Applicants' assignee, Quay, and a third party, Klaveness et al. Indeed, in those proceedings, Applicants filed a request pursuant to 37 C.F.R. § 1.642 to add the Quay '094 and '751 patents to the interference proceedings contingent upon the Administrative Patent Judge's determination that the Quay '094 and '751 patent claims were adequately described and enabled. The Administrative Patent Judge denied this request and directed Applicants to request new interferences regarding these patents. Consequently, Applicants have filed the instant request.[1]

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[1] Applicants believe that Klaveness et al. are not a proper party to the interference requested herein because, as explained in Schneider et al.'s preliminary motions in the above-referenced interferences, Klaveness et al. only describe and enable cross-linked or polymerized structures which are referred to as microballoons in Applicants' specification. It should also be noted that both Quay and Klaveness et al. filed preliminary motions which also contend that Quay and Klaveness et al. should not be in the same interference.

2. Presentation Of Proposed Count Under 37 C.F.R. § 1.607(a)(2)

For the purposes of this rule, the following proposed count is believed to define the claimed interfering subject matter between Applicants' application and the '751 and '688 patents, which is patentable to the Applicants:

Count 1

> Contrast media for ultrasound imaging comprising gaseous microbubbles comprising octafluoropropane or decafluorobutane. **['751 claims 2 and 3]**
>
> or
>
> A biocompatible ultrasound contrast agent comprising perfluoropropane, wherein a portion of said perfluoropropane is present as gaseous microbubbles suspended in a carrier. **['751 claim 5]**
>
> or
>
> A biocompatible ultrasound contrast agent contrast agent comprising perfluorobutane, wherein a portion of said perfluorobutane is present as gaseous microbubbles suspended in a carrier. **['751 claim 9]**
>
> or
>
> A biocompatible ultrasound contrast agent containing gas-filled liposomes, the improvement comprising including microbubbles of at least one gaseous fluorine-containing chemical in said liposomes, wherein the fluorine-containing chemical is selected from the group consisting of perfluoropropane or perfluorobutane, and mixtures thereof. **['751 claim 13]**
>
> or
>
> A biocompatible ultrasound contrast agent containing a suspension of encapsulated air-filled microspheres, the improvement comprising replacing all or a portion of the air with a chemical selected from the group consisting of perfluoropropane and perfluorobutane. **['751 claim 15]**
>
> or

A biocompatible ultrasound contrast agent containing a suspension of crystals in a saccharide diluent, the improvement comprising providing microbubbles of a perfluoropropane or perfluorobutane in said suspension. **['751 claim 19]**

or

A biocompatible ultrasound contrast agent containing an emulsion of highly fluorinated organic compounds, the improvement comprising providing microbubbles of perfluoropropane or perfluorobutane in said emulsion. **['751 claim 21]**

or

Biocompatible ultrasound contrast media comprising free gas microbubbles of a fluorine containing hydrocarbon or sulfur hexafluoride. **['688 claims 1 and 3]**

or

A contrast agent comprising stabilized microbubbles, said stabilized microbubbles comprising a physiologically acceptable gas selected from the group consisting of freons, halogenated hydrocarbons, and fluorinated gases, said stabilized microbubbles being stabilized at least in part by a surfactant. **[Applicants' claim 1]**

In making this request for interference and suggesting this count, Applicants are neither explicitly nor implicitly supporting or acknowledging the patentability of the '751 or '688 patent claims.[2] Specifically, Applicants contend that the Quay '751 and '688 patents only adequately describe and enable contrast agents consisting of "free gas microbubbles" as that term is commonly understood in the art (e.g., microbubbles which are not stabilized, by, for example, surfactants or other surface active agents, not encapsulated, and not surrounded by a tangible membrane). However, many of the Quay '751 patent claims are not expressly

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[2] Applicants are also not explicitly nor implicitly supporting or acknowledging that here are no separately patentable inventions within the proposed count but instead propose this count in order to comply with the rules requiring the initial count to correspond to the broadest issued patent claims. 37 C.F.R. § 1.606.

limited to "free gas microbubbles." Furthermore, Quay is now asserting that the phrase "free gas microbubbles," which appears in many of the '688 patent claims in issue, encompasses contrast agents including microbubbles stabilized by lipids, as well as microballoons or microspheres encapsulated by proteins.[3] Consequently, given the broad language of certain Quay '751 patent claims and Quay's new, broad construction of its "free gas microbubble" claims, the '751 and '688 patent claims interfere with the claims of the instant application.

Applicants' proposed Count 1 is in alternative claim format. The first alternative ("section 1") is taken from Quay '751 claims 2 and 3; the second alternative ("section 2") is taken from Quay '751 claim 5; the third alternative ("section 3") is taken from '751 claim 9; the fourth alternative ("section 4") is taken from '751 claim 13; the fifth alternative ("section 5") is taken from '751 claim 15; the sixth alternative ("section 6") is taken from '751 claim 19; the seventh alternative ("section 7") is taken from '751 claim 21; the eighth alternative ("section 8") is taken from Quay '688 claims 1 and 3; and the ninth alternative ("section 9") is taken from Applicants' claim 1.

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[3] During reexamination of related U.S. Patent No. 5,558,094 (the "'094 patent") Quay advanced a very broad definition of the phrase "free gas microbubbles." Specifically, Quay adopted a definition of "free gas microbubbles" that encompasses "preparations including surfactants and stabilizers (including lipids and proteins)," but excluding "microbubbles which possess a solid or hardened shell." October 2, 1998 Response In Reexamination No. 90/004,656 at 16; May 12, 1998 Office Action In Reexamination No. 90/004,656 at 4. See also, January 20, 1998 Response in the '751 patent's Reexamination No. 90/004,675, at 5. Applicants contend that this definition is not supported by the Quay '751 and '688 patent specifications, which only adequately describe and enable contrast agents containing gas microbubbles which are neither stabilized (e.g., by a surface active agent such as a surfactant) nor encapsulated (e.g., by a protein or polymeric membrane). However, if this broad definition is applied to the free gas microbubble claims, they would appear, on their face, to interfere with Applicants' claims.

3. Identification Of Claims Of The '751 And '688 Patents That Correspond To The Proposed Count Under 37 C.F.R. § 1.607(a)(3)

a. Identification Of '751 Patent Claims That Correspond To The Proposed Count

Applicants identify the following '751 patent claims as corresponding to proposed Count 1:

Proposed Count	'751 Patent Claims That Correspond To Proposed Count
Count 1	2, 3, 5-7, 9-11, 13-16, 18-22 (which are confirmed in a reexamination certificate)

'751 patent claim 2 corresponds to the first portion of the proposed count. Claim 2, which is dependent upon cancelled claim 1, requires that the contrast media comprise gaseous microbubbles comprising octafluoropropane, which is encompassed by section 1 of the proposed count. Thus, the recited microbubbles of octafluoropropane are encompassed by the first section of the proposed count and claim 2 corresponds to the proposed count.

Claim 3 also corresponds to the proposed count. It includes all of the limitations of claim 1 and further limits the gas to decafluorobutane. This gas required by claim 3 is encompassed by the first count section's recitation of the gas. Thus, claim 3 corresponds to the proposed count.

Claims 5, 6 and 7 depend from claim 4 and further specify that the perfluoropropane is present as gaseous microbubbles suspended in a carrier, that the carrier is an aqueous liquid, or that the microbubbles have a recited diameter. These limitations are encompassed by section 2 of the count, which simply requires that the contrast agent "comprise"

perfluoropropane, regardless of additional components or size. Thus, claims 5, 6 and 7 correspond to section 2 of the proposed count.

Claims 9-11 depend directly or indirectly from claim 8 and add the same additional limitations as claims 5-7. These limitations are encompassed by the "comprising" language of section 3 of the proposed count. Therefore, claims 9-11 correspond to the proposed count.

Claims 13-16 and 18-21 are directed to specific types of biocompatible ultrasound contrast agents containing perfluoropropane or perfluorobutane. Indeed, claims 13-14 require gas-filled liposomes including gaseous microbubbles and correspond to section 4 of the count, claims 15, 16 and 18 require a suspension of encapsulated gas filled microspheres and correspond to section 5 of the count, claims 19-20 require a suspension of crystals in a saccharide diluent which include gas microbubbles and correspond to section 6 of the count, and claim 21 requires an emulsion of highly fluorinated organic compounds including gas microbubbles and corresponds to section 7 of the count. Therefore, claims 13-16 and 18-21 correspond to the proposed count also.

Claim 22 like the first section of the proposed count, requires an ultrasound contrast agent including a perfluoropropane or a perfluorobutane. Claim 22 also requires that perfluoropropane or perfluorobutane is provided within the microbubbles of the suspension. These additional requirements are encompassed by the "comprising" language of section 1 of the count. Thus, claim 22 corresponds to the proposed count.

b. Identification Of '688 Patent Claims That Correspond To The Proposed Count

Applicants identify the following '688 patent claims as corresponding to proposed Count 1:

Proposed Count	'688 Patent Claims That Correspond To Proposed Count
Count 1	1-16

Claim 1 of the '688 patent is identical to the eighth section of the proposed count except that it requires one of the two alternative types of gases recited in the count. Thus, claim 1 corresponds to the proposed count. Claim 2 includes all of the limitations of claim 1 and further requires a suspension of free gas bubbles smaller than 8 microns in a biocompatible aqueous liquid vehicle. As this additional limitation is encompassed by the "comprising" language of section 8 of the count, claim 2 corresponds to the proposed count.

Claims 3 and 16 are identical to the eighth section of the proposed count except that claim 3 is limited to sulfur hexafluoride, and claim 16 is limited to dodecafluoropentane. The sulfur hexafluoride of claim 3 is one of the types of gases explicitly recited in this section of the count. Similarly, the dodecafluoropentane of claim 16 is a specific fluorine-containing hydrocarbon, the other type of gas recited in section 8 of the proposed count. Therefore, these claims are encompassed by and correspond to the proposed count.

Claims 4-11 depend from claim 1 and require hexafluoropropylene, octafluoropropane, hexafluoromethane, octafluoro-2-butene, hexafluoro-2-butyne, hexafluoro-buta-1,3-diene, octafluorocyclobutane, or decafluorobutane. As these are specific, fluorine-containing hydrocarbons, claims 4-11 are encompassed by and correspond to the section 8 of

the proposed count. Similarly, claims 12 and 13, which depend from claim 1 and include limitations specifying the size of the free gas microbubbles or requiring that the free gas-microbubbles are suspended in an aqueous liquid vehicle, are encompassed by the "comprising" language of section 8 of the count. Thus, claims 12 and 13 correspond to the proposed count.

Like the proposed count, claims 14 and 15 require biocompatible ultrasound contrast media comprising free gas microbubbles of a fluorine containing hydrocarbon. Claim 14 also requires that: 1) the free gas microbubbles are in solution; and 2) the gas used have a Q coefficient greater than 30. Similarly, claim 15 requires that: (1) the free gas microbubbles are in solution; and (2) the persistence of the free gas microbubbles is sufficient to permit travel to the left heart without dissolution after peripheral intravenous infusion. These limitations are encompassed by the "comprising" language of section 8 of the proposed count and hence are subsets of the count. Thus, claims 14 and 15 correspond to the proposed count also.

4. Compliance With 37 C.F.R. § 1.607(a)(4)

a. Identification of Schneider Pending Application Claims Corresponding To The Proposed Count

Applicants identify the following pending Schneider claims as corresponding to proposed Count 1:

Proposed Count	Schneider Pending Claims That Correspond To Proposed Count
Count 1	1-26

Applicants' claim 1 corresponds exactly to the ninth section of the proposed count.

Applicants' claim 2 is the same as claim 1 except that it specifies that the gas is a freon. This gas is encompassed by section 9 of the proposed count and thus claim 2 corresponds to the proposed count.

Claims 3-26 are dependent upon claim 1 or claim 2 and thus they are encompassed by, and hence correspond to, the proposed count (i.e., section 9) for the same reasons that claim 1 and 2 correspond to the proposed count. Specifically, claim 3 specifies that the stabilized microbubbles of claim 1 are suspended in a carrier. Claim 4 specifies that the stabilized microbubbles of claim 1 are suspended in an aqueous liquid carrier. Claim 5 specifies the size of the stabilized microbubbles of claim 1. Claim 6 specifies that the stabilized microbubbles have a certain stability and resistance to pressure changes. Claims 7 through 26 specify the gases of claims 1 or 2. Since claims 1 and 2 are encompassed by at least section 9 of the proposed count, these dependent claims (i.e., claims 3-26) which add these additional limitations to claims 1 and 2 are also encompassed by the proposed count and should be corresponded to it.

5. **Application Of The Terms Of The Schneider Claims To The Disclosure Of The Application Under 37 C.F.R. § 1.607(a)(5)[4]**

Application of the claim terms to the Applicants' disclosure is as follows:

Claim No.	Claim Element	Support in Applicant's Specification
All	A contrast agent comprising stabilized microbubbles. . .	Support for this element is found throughout the specification, particularly at: p. 1 ("The present invention concerns media adapted for injection into living bodies, e.g., for the purpose of ultrasonic echography and, more particularly, injectable liquid compositions comprising microbubbles of . . .physiologically acceptable gases as stable dispersions or suspensions in an aqueous liquid carrier. These compositions are mostly usable as contrast agents in ultrasonic echography to image the inside of blood-stream vessels and other cavities of living beings, e.g. human patients and animals.") p. 7 ("Practically, to achieve the suspensions of microbubbles according to the invention, one may start with liposomes suspensions or solutions. . . Then air or gas is introduced into the liposome solution so that a suspension of microbubbles will form, said suspension being stabilized by the presence of the surfactants in lamellar form.") (emphasis added)

[4] The claims identified as corresponding to the proposed count are all pending in the Schneider application, and thus 37 C.F.R. § 1.607(5) does not apply. Nevertheless, Applicants have provided the showing required by this Subsection of Rule 1.607.

Claim No.	Claim Element	Support in Applicant's Specification
		pp. 2-3 ("For instance, injecting into the blood-stream of living bodies suspensions of gas microbubbles or microballoons (in the range of 0.5 to 10 μm)in a carrier liquid will strongly reinforce ultrasonic echography imaging, thus aiding in the visualization of internal organs. Imaging of vessels and internal organs can strongly help in medical diagnosis, for instance for the detection of cardiovascular and other diseases.") p. 2 ("One notable application for such dispersions is to be injected into living beings, for instance for ultrasonic echography and other medical applications.") p. 2 ("In this disclosure, the term "microbubble" specifically designates air or gas globules in suspension in a liquid which generally results from the introduction therein of air or a gas in divided form, the liquid preferably also <u>containing surfactants or tensides to control the surface properties thereof and the stability of the bubbles</u>. More specifically, one may consider that the internal volume of the microbubbles is limited by the gas/liquid interface, or in other words, the microbubbles are only bounded by a rather evanescent envelope involving the molecules of the liquid and surfactant loosely bound at the gas to liquid junction boundary.") (emphasis added) p. 45 ("In the Examples to be found hereafter there is disclosed the testing of echogenic microbubbles. . .filled with a number of different gases and mixtures thereof, and the corresponding resistance thereof to pressure increases, both in vivo and in vitro.")

Claim No.	Claim Element	Support in Applicant's Specification
All	. . .said stabilized microbubbles comprising a physiologically acceptable gas selected from the group consisting of freons, halogenated hydrocarbons, and fluorinated gases. . . or . . .said stabilized microbubbles comprising a physiologically acceptable gas that is a freon. . .	Support for this element is found throughout the specification, particularly at: p. 1 ("The present invention concerns. . .injectable liquid compositions comprising microbubbles of . . . physiologically acceptable gases.") pp. 15-16 ("The gases in the microbubbles of the present invention can include. . . physiologically acceptable gases like. . .freon and mixtures thereof.") (emphasis added) p. 51 ("The gaseous species which particularly suit the invention are, for instance, halogenated hydrocarbons like the freons and stable fluorinated chalcogenides like SF_6, SeF_6 and the like.") (emphasis added) p. 52, particularly item 3 (disclosing stabilized microbubbles filled with a physiologically acceptable freon, a halogenated hydrocarbon, or a fluorinated gas such as SF_6, CF_4, $CBrF_3$, C_4F_8, $CClF_3$, CCl_2F_2, C_2F_6, C_3F_8, C_4F_6, C_5F_{10}, C_5F_{12}, C_2ClF_5, $CBrClF_2$, $C_2Cl_2F_4$, CBr_2F_2 and C_4F_{10}) p. 45 ("This problem has now been solved by using gases or gas mixtures in conformity with the criteria outlined in the embodiments below. Briefly, it has been found that when the echogenic microvesicles are made in the presence of a gas, respectively, are filled at least in part with a gas having physical properties in conformity with the equation below, the microvesicles remarkably resist pressure. . .")

Claim No.	Claim Element	Support in Applicant's Specification
		Examples, particularly Examples 21-23 (disclosing stabilized microbubbles of a physiologically acceptable freon, a halogenated hydrocarbon, or a fluorinated gas)
1, 3-8, 11-22	. . .said stabilized microbubbles being stabilized, at least in part, by a surfactant. . .	Support for this element is found throughout the specification, particularly at: p.7 ("Practically, to achieve the suspensions of microbubbles according to the invention, one may start with liposomes suspensions or solutions. . . Then air or gas is introduced into the liposome solution so that a suspension of microbubbles will form, said suspension being stabilized by the presence of the surfactants in lamellar form.") (emphasis added) p. 6 ("The term "lamellar form" defining the condition of at least a portion of the surfactant or surfactants of the present composition indicates that the surfactants, in strong contrast with the microparticles of the prior art (for instance EP-A-0123235), are in the form of thin films involving one or more molecular layers (in laminate form).")

Claim No.	Claim Element	Support in Applicant's Specification
		p. 2 ("In this disclosure, the term "microbubble" specifically designates air or gas globules in suspension in a liquid which generally results from the introduction therein of air or a gas in divided form, the liquid preferably also containing surfactants or tensides to control the surface properties thereof and the stability of the bubbles. More specifically, one may consider that the internal volume of the microbubbles is limited by the gas/liquid interface, or in other words, the microbubbles are only bounded by a rather evanescent envelope involving the molecules of the liquid and surfactant loosely bound at the gas to liquid junction boundary.") (emphasis added) p. 7 ("air or a gas is introduced into the liposome solution so that a suspension of microbubbles will form, said suspension being stabilized by the presence of the surfactants in lamellar form.") (emphasis added) pp. 6-7 ("In this invention, one preferably uses the lipids commonly used for making liposomes, for instance the lecithins and other tensides disclosed in more detail hereafter, but this does in no way preclude the use of other surfactants provided they can be formed into layers or films.") p. 10 ("The tensides or surfactants which are convenient in this invention can be selected from all amphipatic compounds capable of forming stable films in the presence of water and gases.")

Claim No.	Claim Element	Support in Applicant's Specification
		p. 11 ("additives may include other surfactants that can be used in admixture with the film forming surfactants and most of which are recited in the prior art discussed in the introduction of this specification") pp. 12-13 ("The present invention naturally also includes dry storable pulverulent blends which can generate the present microbubble containing dispersions upon simple admixing with water or an aqueous carrier phase. Preferably such dry blends or formulations will contain all solid ingredients necessary to provide the desired microbubbles suspensions upon the simple addition of water, i.e., principally the surfactants in lamellar form containing trapped or adsorbed therein the air or gas required for microbubble formation, and accessorily the other non-film forming surfactants, the viscosity enhancers and stabilizers and possibly other optional additives.") (emphasis added) pp. 45-46 ("the preferred microbubbles are those of the compositions disclosed herein (e.g., supra) and in PCT/EP91/00620; these microbubbles are advantageously formed from an aqueous liquid and a dry powder (microvesicle precursors) containing lamellarized freeze-dried phospholipids and stabilizers; the microbubbles are developed by agitation of this powder in admixture with the aqueous liquid carrier.")

Claim No.	Claim Element	Support in Applicant's Specification
		p. 14 (" . . .the stability of the bubbles depends on the surfactant in lamellar form rather than on the presence of stabilizers or viscosity enhancers like in the prior art. This property is advantageous in regard to imaging test reproducibility as the bubbles are not affected by dilution with blood upon injection into a patient.") p. 44 ("Despite the many progresses achieved regarding the stability under storage of aqueous microbubble suspensions, this being either in the precursor or final preparation stage, there still remained until now the problem of vesicle durability when the suspensions are exposed to overpressure, e.g., pressure variations such as that occurring after injection in the blood stream of a patient and consecutive to heart pulses, particularly in the left ventricle.") p. 45 ("In the Examples to be found hereafter there is disclosed the testing of echogenic microbubbles. . .filled with a number of different gases and mixtures thereof, and the corresponding resistance thereof to pressure increases, both in vivo and in vitro.") pp. 16-19 (disclosing various embodiments of microbubbles stabilized, at least in part, by a film forming surfactant) Examples (particularly Examples 1-9 and 21-23, disclosing contrast agents comprising microbubbles stabilized, at least in part, by a film forming surfactant)

Claim No.	Claim Element	Support in Applicant's Specification
3	. . .wherein said stabilized microbubbles are suspended in a carrier.	Support for this element is found throughout the specification, particularly at: p. 1 ("The present invention concerns media adapted for injection into living bodies, e.g., for the purpose of ultrasonic echography and, more particularly, injectable liquid compositions comprising microbubbles of air or physiologically acceptable gases as stable dispersions or suspensions in an aqueous liquid carrier.") (emphasis added) p. 2 ("The present invention also concerns stable dispersions or compositions of gas filled microvesicles in aqueous carrier liquids. These dispersions are generally usable for most kinds of applications requiring gases homogeneously dispersed in liquids. One notable application for such dispersions is to be injected into living beings, for instance for ultrasonic echography and other medical applications.") (emphasis added) pp. 2-3 ("For instance, injecting into the blood-stream of living bodies suspensions of gas microbubbles. . .(in the range of 0.5 to 10 μm) in a carrier liquid will strongly reinforce ultrasonic echography imaging, thus aiding in the visualization of internal organs. Imaging of vessels and internal organs can strongly help in medical diagnosis, for instance for the detection of cardiovascular and other diseases.") (emphasis added)

Claim No.	Claim Element	Support in Applicant's Specification
		p. 12 ("The aqueous carrier in this invention is mostly water with possibly small quantities of physiologically compatible liquids such as isopropanol, glycerol, hexanol and the like (see for instance EP-A-052575). In general the amount of the organic hydrosoluble liquids will not exceed 5-10% by weight.") (emphasis added) p. 7 ("air or a gas is introduced into the liposome solution so that a suspension of microbubbles will form, said suspension being stabilized by the presence of the surfactants in lamellar form.") (emphasis added) p. 10 ("Microbubbles suspensions formed by applying gas pressure on a dilute solution of laminated lipids in water (0.1-10% by weight) and thereafter suddenly releasing the pressure have an even higher bubble concentration, e.g., in the order of 10^{10} - 10^{11} bubbles/ml.") (emphasis added) p. 12 ("The present invention naturally also includes dry storable pulverant blends which can generate the present microbubble containing dispersions upon simple admixing with water or an aqueous carrier phase.") (emphasis added) p. 14 ("The resulting microbubble suspensions (bubble in the 0.5-10 μm range) are extraordinarily stable with time, the count originally measured at start staying unchanged or only little changed for weeks and even months.") (emphasis added)

Claim No.	Claim Element	Support in Applicant's Specification
		p. 44 ("Despite the many progresses achieved regarding the stability under storage of aqueous microbubble suspensions, this being either in the precursor or final preparation stage, there still remained until now the problem of vesicle durability when the suspensions are exposed to overpressure, e.g., pressure variations such as that occurring after injection in the blood stream of a patient and consecutive to heart pulses, particularly in the left ventricle.") (emphasis added) p. 46 ("the microbubbles are developed by agitation of this powder in admixture with the aqueous liquid carrier.") p. 46 ("In order to carry out the method of the present invention, i.e., to form or fill the microvesicles, whose suspensions in aqueous carriers constitute the desired echogenic additives, with the gases according to the foregoing relation, one can either use, as a first embodiment, a two step route consisting of (1) making the microvesicles from appropriate starting materials by any suitable conventional technique in the presence of any suitable gas, and (2) replacing this gas originally used (first gas) for preparing the microvesicles with a new gas (second gas) according to the invention (gas exchange technique).") (emphasis added) pp. 16-19 (disclosing various embodiments of contrast agents comprising suspensions of surfactant stabilized microbubbles in a carrier)

Claim No.	Claim Element	Support in Applicant's Specification
		Examples (particularly Examples 1-9 and 21-23 disclosing contrast agents comprising suspensions of surfactant stabilized microbubbles in a carrier) pp. 52-54 (disclosing various embodiments of contrast agents comprising suspensions of surfactant stabilized microbubbles in a carrier)
4	. . .wherein said stabilized microbubbles are suspended in an aqueous liquid carrier.	Support for this element is found throughout the specification, particularly at: p. 1 ("The present invention concerns media adapted for injection into living bodies, e.g., for the purpose of ultrasonic echography and, more particularly, injectable liquid compositions comprising microbubbles of air or physiologically acceptable gases as stable dispersions or suspensions in an aqueous liquid carrier.") (emphasis added) p. 2 ("The present invention also concerns stable dispersions or compositions of gas filled microvesicles in aqueous carrier liquids. These dispersions are generally usable for most kinds of applications requiring gases homogeneously dispersed in liquids. One notable application for such dispersions is to be injected into living beings, for instance for ultrasonic echography and other medical applications.") (emphasis added)

Claim No.	Claim Element	Support in Applicant's Specification
		p. 12 ("The aqueous carrier in this invention is mostly water with possibly small quantities of physiologically compatible liquids such as isopropanol, glycerol, hexanol and the like (see for instance EP-A-052575). In general the amount of the organic hydrosoluble liquids will not exceed 5-10% by weight.") (emphasis added) pp. 13-14 ("for preparing a gas or air microbubble suspension for ultrasonic imaging, one simply dissolves a known weight of the dry pulverulent formulation in a sterile aqueous phase, e.g., water or a physiologically acceptable medium. The amount of powder will depend on the desired concentration of bubbles in the injectable product, a count of about 10^8 -10^9 bubbles/ml being generally that from making a 5-20% by weight solution of the powder in water.") (emphasis added) p. 2 ("In this disclosure, the term "microbubble" specifically designates air or gas globules in suspension in a liquid which generally results from the introduction therein of air or a gas in divided form, the liquid preferably also containing surfactants or tensides to control the surface properties thereof and the stability of the bubbles. More specifically, one may consider that the internal volume of the microbubbles is limited by the gas/liquid interface, or in other words, the microbubbles are only bounded by a rather evanescent envelope involving the molecules of the liquid and surfactant loosely bound at the gas to liquid junction boundary.") (emphasis added)

Claim No.	Claim Element	Support in Applicant's Specification
		pp. 2-3 ("For instance, injecting into the blood-stream of living bodies suspensions of gas microbubbles . . . (in the range of 0.5 to 10 μm) in a carrier liquid will strongly reinforce ultrasonic echography imaging, thus aiding in the visualization of internal organs." (emphasis added) p. 12 ("The present invention naturally also includes dry storable pulverant blends which can generate the present microbubble containing dispersions upon simple admixing with water or an aqueous carrier phase." (emphasis added) pp. 45-46 ("the preferred microbubbles are those of the compositions disclosed herein (e.g., supra); these microbubbles are advantageously formed from an aqueous liquid and a dry powder (microvesicle precursors) containing lamellarized freeze-dried phospholipids and stabilizers; the microbubbles are developed by agitation of this powder in admixture with the aqueous liquid carrier.") (emphasis added) p. 46 ("In order to carry out the method of the present invention, i.e., to form or fill the microvesicles, whose suspensions in aqueous carriers constitute the desired echogenic additives, with the gases according to the foregoing relation, one can either use, as a first embodiment, a two step route consisting of (1) making the microvesicles from appropriate starting materials by any suitable conventional technique in the presence of any suitable gas, and (2) replacing this gas originally used (first gas) for preparing the microvesicles with a new gas (second gas) according to the invention (gas exchange technique).") (emphasis added)

Claim No.	Claim Element	Support in Applicant's Specification
		p. 47 ("Hence, in one preferred case where microbubbles are to be formed from an aqueous phase and dry laminarized phospholipids, e.g., powders of dehydrated lyophilized liposomes plus stabilizers, which powders are to be subsequently dispersed under agitation in a liquid aqueous carrier phase, it is advantageous to store this dry powder under an atmosphere of a gas selected according to the invention. A preparation of such kind will keep indefinitely in this state and can be used at any time for diagnosis, provided it is dispersed into sterile water before injection.") (emphasis added) p. 48 ("In the description of the Experimental part that follows (Examples), gas-filled microvesicles suspended in water or other aqueous solutions have been subjected to pressures over that of ambient.") (emphasis added) pp. 16-19 (disclosing various embodiments of contrast agents comprising suspensions of surfactant stabilized microbubbles in an aqueous liquid carrier) Examples (particularly Examples 1-9 and 21-23 disclosing contrast agents comprising suspensions of surfactant stabilized microbubbles in an aqueous liquid carrier) pp. 52-54 (disclosing various embodiments of contrast agents comprising suspensions of surfactant stabilized microbubbles in an aqueous liquid carrier)

Claim No.	Claim Element	Support in Applicant's Specification
5	. . .wherein said stabilized microbubbles are between 0.5 and 10 microns in size.	pp. 2-3 ("For instance, injecting into the blood-stream of living bodies suspensions of gas microbubbles . . . (in the range of 0.5 to 10 μm) in a carrier liquid will strongly reinforce ultrasonic echography imaging, thus aiding in the visualization of internal organs. Imaging of vessels and internal organs can strongly help in medical diagnosis, for instance for the detection of cardiovascular and other diseases.") (emphasis added) p. 6 ("for efficiently imaging certain organs, e.g., the left heart, bubbles smaller than 50 μm, preferably in the range of 0.5-10 μm, are required; with larger bubbles, there are risks of clots and consecutive emboly. ") (emphasis added) pp. 9-10 ("Actually making very dilute aqueous solutions (0.1-10% by weight) of freeze-dried liposomes stabilized with, for instance, a 5:1 to 10:1 weight ratio of lactose to lipid enables to produce aqueous microbubbles suspensions counting 10^8 -10^9 microbubbles/ml (size distribution mainly 0.5-10 μm) which are stable for at least a month (and probably much longer) without significant observable change.") (emphasis added) p. 14 ("The resulting microbubble suspensions (bubble in the 0.5-10 μm range) are extraordinarily stable with time, the count originally measured at start staying unchanged or only little changed for weeks and even months;") (emphasis added)

Claim No.	Claim Element	Support in Applicant's Specification
		p. 17, particularly item 6 ("The composition of embodiment 1, containing about 10^8-10^9 bubbles of 0.5-10μm size/ml, said concentration showing little or substantially no variability under storage for at least a month.") See also item 5. (emphasis added) Examples (particularly Examples 3-9 disclosing suspensions of surfactant stabilized microbubbles with average diameters of less than 10 microns.) See also Examples 21-23 (disclosing suspensions of surfactants stabilized microbubbles sufficiently small to allow imaging of the left heart - e.g., smaller than 10 microns).
6	. . .wherein the stabilized microbubbles are sufficiently stable and resistant to pressure changes that they survive in the bloodstream long enough that they may be peripherally intravenously injected, travel through the right heart, through the lungs, and into the left heart without substantially dissolving.	Examples, particularly Example 3 (disclosing opacification of the left heart and clear outlining of the endocardium after peripheral intravenous injection "thereby confirming that the microbubbles (or at least a significant part of them) were able to cross the pulmonary capillary circulation" and image the left heart) and Examples 22 and 23 (disclosing successful imaging of the left heart after peripheral intravenous injection, establishing that the microbubbles are sufficiently stable and resistant to pressure changes that they survive in the bloodstream long enough that they may be used to image the left cardiac chambers without dissolving.) (emphasis added)

Claim No.	Claim Element	Support in Applicant's Specification
		p. 45 ("This problem has now been solved by using gases or gas mixtures in conformity with the criteria outlined in the embodiments shown below. Briefly, it has been found that when the echogenic microvesicles are made in the presence of a gas, respectively are filled at least in part with a gas, having physical properties in conformity with the equation below, then the microvesicles remarkably resist pressure > 60 Torr after injection for a time sufficient to obtain reproducible echographic measurements.") (emphasis added) p. 45 ("In the Examples to be found hereafter there is disclosed the testing of echogenic microbubbles . . . (see the Tables) filled with a number of different gases and mixtures thereof, and the corresponding resistance thereof to pressure increases, both in vivo and in vitro.") (emphasis added) p. 14 ("Another advantage of the bubbles of this invention versus the microbubbles of the prior art surrounded by a rigid but breakable membrane which may irreversibly fracture under stress is that when the present suspensions are subject to sudden pressure changes, the present bubbles will momentarily contract elastically and then resume their original shape when the pressure is released. This is important in clinical practice when the microbubbles are pumped through the heart and therefore are exposed to alternating pressure pulses.") (emphasis added)

Claim No.	Claim Element	Support in Applicant's Specification
		p. 44 ("Despite the many progresses achieved regarding the stability under storage of aqueous microbubble suspensions, this being either in the precursor or final preparation stage, there still remained until now the problem of vesicle durability when the suspensions are exposed to overpressure, e.g., pressure variations such as that occurring after injection in the blood stream of a patient and consecutive to heart pulses, particularly in the left ventricle.") (emphasis added) p. 14 ("It has also been found that the microbubbles suspensions of this invention can be diluted with very little loss in the number of microbubbles to be expected from dilution, i.e., even in the case of high dilution ratios, e.g., $1/10^2$ to $1/10^4$, the microbubble count reduction accurately matches with the dilution ratio. This indicates that the stability of the bubbles depends on the surfactant in lamellar form rather than on the presence of stabilizers or viscosity enhancers like in the prior art. This property is advantageous in regard to imaging test reproducibility as the bubbles are not affected by dilution with blood upon injection into a patient.") (emphasis added) p. 14 ("The resulting microbubble suspensions (bubble in the 0.5-10 μm range) are extraordinarily stable with time, the count originally measured at start staying unchanged or only little changed for weeks and even months;") (emphasis added)

Claim No.	Claim Element	Support in Applicant's Specification
7, 9, 11, 14-22	. . .wherein the physiologically acceptable freon is selected from the group consisting of CF_4, $CBrF_3$, C_4F_8, $CClF_3$, C_2F_6, C_3F_8, C_4F_6, C_2ClF_5, $CBrClF_2$, $C_2Cl_2F_4$, C_5F_{10}, C_5F_{12}, and C_4F_{10}.	Support for this element is found throughout the specification, particularly at: p. 52, particularly item 3 (e.g. "The method of embodiment, in which the physiologically acceptable gas used is selected from SF_6 or Freon® such CF_4, $CBrF_3$, C_4F_8, $CClF_3$, CCl_2F_2, C_2F_6, C_3F_8, C_4F_6, C_5F_{10}, C_5F_{12}, C_2ClF_5, CBr, ClF_2, $C_2Cl_2F_4$, CBr_3F_2 and C_4F_{10}.") Examples 21-23 (disclosing surfactant stabilized microbubbles containing physiologically acceptable freons such as $CBrF_3$, C_4F_8, $CHClF_2$ and C_4F_8.) p. 51 ("The gaseous species which particularly suit the invention are, for instance, halogenated hydrocarbons like the freons. . . [listing specific gases].") (emphasis added) pp. 15-16 ("The gases in the microbubbles of the present invention can include. . .physiologically acceptable gases like. . .freon and mixtures thereof. . . [listing specific gases]. . .")(emphasis added) p. 45 ("This problem has now been solved by using gases or gas mixtures in conformity with the criteria outlined in the embodiments below. Briefly, it has been found that when the echogenic microvesicles are made in the presence of a gas, respectively, are filled at least in part with a gas having physical properties in conformity with the equation below, the microvesicles remarkably resist pressure. . .")

Claim No.	Claim Element	Support in Applicant's Specification
		p. 1 ("The present invention concerns. . .injectable liquid compositions comprising microbubbles of air or physiologically acceptable gases.")
8, 10	. . .the physiologically acceptable fluorinated gas is selected from the group consisting of SF_6, SeF_6, CF_4, $CBrF_3$, C_4F_8, $CClF_3$, C_2F_6, C_3F_8, C_4F_6, C_2ClF_5, $CBrClF_2$, $C_2Cl_2F_4$, C_5F_{10}, C_5F_{12}, and C_4F_{10}.	Support for this element is found throughout the specification, particularly at: p. 52, particularly item 3 (e.g. "The method of embodiment, in which the physiologically acceptable gas used is selected from SF_6 or Freon® such as CF_4, $CBrF_3$, C_4F_8, $CClF_3$, CCl_2F_2, C_2F_6, C_3F_8, C_4F_6, C_5F_{10}, C_5F_{12}, C_2ClF_5, CBr, ClF_2, $C_2Cl_2F_4$, CBr_3F_2 and C_4F_{10}.") Examples 21-23 (disclosing surfactant stabilized microbubbles containing fluorinated gases such as $CBrF_3$, SF_6, C_4F_8, $CHClF_2$ and C_4F_8.) p. 51 ("The gaseous species which particularly suit the invention are, for instance, halogenated hydrocarbons like the freons and stable fluorinated chalcogenides like SF_6, SeF_6 and the like. . .[listing specific gases]") (emphasis added) pp. 15-16 ("The gases in the microbubbles of the present invention can include. . .physiologically acceptable gases like. . .freon and mixtures thereof. . .[listing specific gases]. . .") (emphasis added)

Claim No.	Claim Element	Support in Applicant's Specification
		p. 45 ("This problem has now beensolved by using gases or gas mixtures in conformity with the criteria outlined in the embodiments below. Briefly, it has been found that when the echogenic microvesicles are made in the presence of a gas, respectively, are filled at least in part with a gas having physical properties in conformity with the equation below, the microvesicles remarkably resist pressure. . .") p. 1 ("The present invention concerns. . .injectable liquid compositions comprising microbubbles of air or physiologically acceptable gases.")

6. Explanation Of How The Requirements Of 35 U.S.C. § 135(b) Are Met Pursuant To 37 C.F.R. § 1.607(a)(6)

This request for interference with the '751 and '688 patents complies with 35 U.S.C. § 135(b) because Applicants had claims to the same or substantially the same subject matter as at least one '751 and '688 patent claim pending in parent applications within one year of the issue dates of the '688 and '751 patents.[5] See, e.g., MPEP § 2307.02 ("under the provisions of 35 U.S.C. § 135(b), an interference will not be declared unless at least one of the claims which were in the application, or a parent application, prior to expiration of the one-year period was for substantially the same subject matter as at least one of the claims of the patent.") Specifically, as shown in the attached charts, Exhibits 2 and 3 hereto, the following Schneider et al. parent applications had claims directed to substantially the same

[5] Within one year of the issue date of the '751 reexamination certificate would also suffice under 35 U.S.C. § 135(b).

subject matter as at least one '751 and '688 patent claim pending no later than one year from the April 25, 1995 and November 12, 1996 issue dates of the '688 and '751 patents: U.S.S.N. 07/991,237, filed December 16, 1992, issued as U.S. Patent No. 5,413,774 on May 9, 1995; U.S.S.N. 08/380,588, filed January 30, 1995, issued as U.S. Patent No. 5,578,292 on November 26, 1996; U.S.S.N. 08/352,108, filed November 30, 1994, issued as U.S. Patent No. 5,556,610 on September 17, 1996; and U.S.S.N. 08/456,385, filed June 1, 1995, issued as U.S. Patent No. 5,658,551 on August 19, 1997.

7. **Compliance With 37 C.F.R. § 1.608(a)**

Applicants declare, in accordance with Rule 608(a), that Applicants are and will be entitled to a judgment in an interference with the '751 and '688 patents based on priority, as is further explained below. The Declaration of Arthur Crawford, submitted herewith, establishes that there is a basis upon which Applicants are entitled to a judgment in an interference proceeding relative to the '751 and '688 patents.

For the subject matter of the proposed count, Applicants are entitled to a priority date of April 2, 1990, the filing date of Applicants' earliest benefit application, EP No. 90810262.7. In contrast, Quay is entitled to an earliest possible effective filing date of September 17, 1991 for both the '751 and '688 patents, the filing date of U.S.S.N. 761,311, the earliest Quay benefit application. Consequently, the earliest possible effective filing date of the Quay '751 and '688 patents is more than a year after Applicants effective filing date.

Conclusion

For the reasons presented above, Applicants request that an interference be declared between its application and Quay's 751 and '688 patents.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Arthur R. Crawford
Reg. No. 25,327

Nixon & Vanderhye, P.C.
1100 North Glebe Road
Arlington, VA 22201
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

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REEXAMINATION CERTIFICATE (3751th)

United States Patent [19]

Quay

[11] B1 5,573,751

[45] Certificate Issued Mar. 9, 1999

[54] **PERSISTENT GASEOUS BUBBLES AS ULTRASOUND CONTRAST MEDIA**

[75] Inventor: **Steven C. Quay**, Los Angeles, Calif.

[73] Assignee: **Sonus Pharmaceuticals, Inc.**, Costa Mesa, Calif.

Reexamination Requests:
No. 90/004,657, Jun. 3, 1997
No. 90/005,000, May 15, 1998

Reexamination Certificate for:

Patent No.:	**5,573,751**
Issued:	**Nov. 12, 1996**
Appl. No.:	**361,118**
Filed:	**Dec. 21, 1994**

Related U.S. Application Data

[62] Division of Ser. No. 71,377, Jun. 4, 1993, Pat. No. 5,393,524, Continuation of Ser. No. 761,311, Sep. 17, 1991, abandoned.

[51] **Int. Cl.**[6] **A61K 49/02**

[52] **U.S. Cl.** **424/9.52**; 424/9.5; 424/9.51; 424/673; 600/458; 514/744; 514/746; 514/752; 514/754; 514/757

[58] **Field of Search** 424/952, 9.5, 9.51, 424/673; 600/458; 514/744, 746, 752, 754, 757

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Primary Examiner—Gary E. Hollinden

[57] **ABSTRACT**

Disclosed herein are agents for enhancing the contrast in an ultrasound image. These agents are extremely small bubbles, or "microbubbles", comprised of specially selected gases. The microbubbles described herein exhibit long life spans in solution and may be produced at a size small enough to traverse the lungs, thus enabling improved ultrasound imaging of the cardiovascular system and other vital organs. Also disclosed herein is a method for selecting gases from which contrast agents may be produced. The method is based on calculations using inherent physical properties of gases and describes a means to associate the properties of a gas with the time for dissolution of a microbubble comprised of the gas.

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REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

The patentability of claims **2, 3, 5, 6, 9 & 10** are confirmed.

Claims **1, 4, 8, 12** and **17** are cancelled.

Claims **7, 11, 13, 14, 15, 19, 21,** and **22** are determined to be patentable as amended.

Claims **16, 18** and **20**, dependent on an amended claim, are determined to be patentable.

7. The contrast agent of claim **[4]** *5* wherein a portion of said microbubbles are less than 8 microns in diameter.

11. The contrast agent of claim **[8]** *9* wherein a portion of said microbubbles are less than 8 microns in diameter.

13. The contrast agent of claim **12** wherein the fluorine-containing chemical is selected from the group consisting of **[perfluoroethane,]** perfluoropropane, perfluorobutane **[, sulfur hexafluoride]** and mixtures thereof.

14. The contrast agent of claim **[12]** *13* wherein said liposomes are less than eight microns in diameter.

15. A biocompatible ultrasound contrast agent containing a suspension of encapsulated air-filled microspheres, the improvement comprising replacing all or a portion of the air with **[at least one gaseous fluorine-containing]** *a* chemical *selected from the group consisting of perfluoropropane and perfluorobutane.*

19. A biocompatible ultrasound contrast agent containing a suspension of crystals in a saccharide diluent, the improvement comprising providing microbubbles of **[a perfluoroethane,]** perfluoropropane**[,]** *or* perfluorobutane **[and sulfur hexafluoride]** *in said suspension.*

21. A biocompatible ultrasound contrast agent containing an emulsion of highly fluorinated organic compounds, the improvement comprising providing microbubbles of *perfluoropropane or perfluorobutane* **[at least one gaseous fluorine containing chemical]** in said emulsion.

22. A biocompatible ultrasound contrast agent containing an air-filled microbubble suspension, the improvement comprising providing **[perfluoroethane,]** perfluorobutane **[,]** *or* perfluoropropane **[or sulfur hexafluoride]** gas within the microbubbles of said suspension.

* * * * *

Exhibit 2
To Request For Interference

135(b) Showing For Quay '751 Patent

The chart below establishes that claims pending in Applicants' parent applications prior to November 12, 1996, the one year anniversary of the original '751 patent issue date,[1] encompass substantially the same subject matter at least one '751 patent claim. An analysis of two of the '751 patent claims and Applicants' claims is provided.

'751 Patent Claim	'751 Patent Claim Elements	Applicants' Claims Pending Before November 12, 1996
8	A biocompatible ultrasound contrast agent comprising perfluorobutane.	• U.S.S.N. 07/991,237 (now U.S. Patent No. 5,413,774), claims filed 12/16/92: 14. Suspensions of gas filled microvesicles distributed in an aqueous carrier liquid to be used as contrast agents in ultrasonic echography, characterized in that the gas is physiologically acceptable and such that at least a portion thereof has a solubility in water, expressed in liter of gas by liter of water under standard conditions, divided by the square root of the molecular weight does not exceed 0.003. [Applicants' claim 14 includes substantially the same subject matter as '751 claim 8. As an initial matter, both '751 claim 8 and Applicants' claim 14 require an ultrasound contrast agent. Moreover, although '751 claim 8 requires perfluorobutane, these gases (e.g., C_4F_8 and C_4F_{10}) are included in and patentably indistinct from the genus defined by Applicants' recited criteria. Indeed, Applicants' claim 3 explicitly recites perfluorobutane (C_4F_8 and C_4F_{10}).[2] Therefore, claim 14 encompasses substantially the same subject matter as '751 claim 8. However, Applicants contend that the claim's microvesicles are separately patentable over the '751 patent claims.]

[1] Applicants contend that the 135(b) date for the '751 claims amended or added during the reexamination proceeding is one year from the issue date of the reexamination certificate confirming those claims. Nevertheless, Applicants have established that claims pending in parent applications within one year of the issue date of the original '751 patent were directed to substantially the same subject matter as at least one '751 patent claim.

[2] Claim 3 recites:

3. The method of claim 1, in which the physiologically acceptable gas used is selected from SF_6, SeF_6, Freon® such as CF_4, $CBrF_3$, C_4F_8, $CClF_3$, CCl_2F_2, C_2F_6, C_2ClF_5, $CBrClF_2$, $C_2Cl_2F_4$, CBr_2F_2 and C_4F_{10}.

'751 Patent Claim	'751 Patent Claim Elements	Applicants' Claims Pending Before November 12, 1996
		• U.S.S.N. 08/352,108, claims filed 11/30/94: 4. The ultrasound contrast medium of claim 3, wherein the fluorine-containing gas is sulfur hexafluoride or octafluorocyclobutane. 3. The ultrasound contrast medium of claim 2, wherein the fluorine-containing gas is selected from the group consisting of SF_6, CF_4, C_2F_6, C_2F_8, C_3F_6, C_3F_8, C_4F_6, C_4F_8, C_4F_{10}, C_5F_{10}, C_5F_{12} and mixtures thereof. 2. The ultrasound contrast medium of claim 1, wherein gas (B) is a fluorine-containing biocompatible gas. 1. An injectable ultrasound contrast medium comprising biocompatible at body temperature gaseous substances which when in suspension in an aqueous carrier liquid containing usual surfactants, additives and stabilizers provide contrast agents for ultrasound echography, characterized in the medium is a mixture of gases (A) and (B) in which, at least one of the gases (B), present in an amount of between 0.5-41% by vol., has a molecular weight greater than 80 daltons and its solubility in water is below 0.0283 ml of gas per ml of water measured under standard conditions, the balance of the mixture being gas A. [Applicants' claims 3 and 4 include substantially the same subject matter as '751 claim 8. Both '751 claim 8 and Applicants' claims encompass an ultrasound contrast agent comprising perfluorobutane. Therefore, Applicants' claims 3 and 4 encompass substantially the same subject matter as '751 claim 8. However, Applicants contend that the claims' "surfactants, additives and stabilizers," and its gas mixtures are separately patentable over the '751 patent claims.] • U.S.S.N. 08/380,588 (now U.S. Patent No. 5,578,292), 10/12/95 Amendment: 28. The contrast agent of claim 27, in which the Freon is selected from the group consisting of CF_4, $CBrF_3$, C_4F_8, $CClF_3$, CCl_2F_2, C_2F_6, C_2ClF_5, $CBrClF_5$, $CBrClF_2$, $C_2Cl_2F_4$, CBr_2F_2 and C_4F_{10}. 27. The contrast agent of claim 26 in which the halogenated hydrocarbon is selected from the group consisting of SF_6 and Freon(s).

'751 Patent Claim	'751 Patent Claim Elements	Applicants' Claims Pending Before November 12, 1996
		26. A contrast agent for ultrasonic echography comprising gas-filled microvesicles suspended in a liquid carrier phase, the microvesicles being either microbubbles bonded [sic-bounded] by an evanescent gas/liquid interfacial closed surface or microballoons bounded by a material envelope, wherein the microvesicles contain a gas mixture of a first gas and a second gas, the second gas being a physiologically acceptable hydrocarbon. [Applicants' claim 28 includes substantially the same subject mater as '751 claim 8. Indeed, both '751 claim 8 and Applicants' claims encompass an ultrasound contrast agent comprising perfluorobutane. However, Applicants contend that the claims' microvesicles, microbubbles, microballoons and gas mixtures are separately patentable over the '751 patent claims.] • U.S.S.N. 08/456,385 (now U.S. Patent No. 5,685,551), 9/16/95 Amendment: 36. A suspension according to claim 36 [sic-35], wherein said gas is a freon. 35. A microbubble suspension comprising gas microbubbles of a physiologically acceptable fluorine-containing entrappable gas. [Applicants' claim 36 includes substantially the same subject matter as '751 claim 8. As an initial matter, both claim 8 of the '751 patent and Applicants' claim encompass microbubbles of a physiologically acceptable freon. Indeed, although '751 claim 8 requires perfluorobutane, these gases (e.g., C_4F_8, C_4F_{10}) are included in and patentably indistinct from the genus physiologically acceptable freon of Applicants' claim. Moreover, as Applicants' claims do not include any use limitations, they certainly encompass use as an ultrasound contrast agent. In any event, this limitation is not believed to be material to patentability. Therefore, claim 36 encompasses substantially the same subject matter as '751 claim 8. However, Applicants contend that the claims' microbubbles are separately patentable over the '751 patent claims.]

'751 Patent Claim	'751 Patent Claim Elements	Applicants' Claims Pending Before November 12, 1996
		• U.S.S.N. 08/456,385 (now U.S. Patent No. 5,658,551), 4/18/95 Amendment 35. (Amended) A microbubble suspension comprising gas microbubbles of a physiologically acceptable, fluorine-containing entrappable gas or a mixture of a fluorine-containing entrappable gas with CO_2, nitrogen or H_2O in a suspension of dissolved or dispersed surfactants, at least one of the surfactants being a film-forming phospholipid present in the suspension at least partially in lamellar or laminar form. [Applicants' claim 35 includes substantially the same subject matter as '751 claim 8. Both claim 8 of the '751 patent and Applicants' claim 35 encompass microbubbles of a physiologically acceptable freon. Indeed, although '751 claim 8 requires perfluorobutane, these gases (e.g., C_4F_8 and C_4F_{10}) are included in and patentably indistinct from the genus physiologically acceptable freon of Applicants' claim. Moreover, as Applicants' claim does not include any use limitations, it certainly encompasses use as an ultrasound contrast agent. In any event, this limitation is not believed to be material to patentability. Therefore, Applicants' claim 35 encompasses substantially the same subject matter as '751 claim 8. However, Applicants contend that the claim's microbubbles, gas mixtures and surfactants are separately patentable over the '751 patent claims.]

'751 Patent Claim	'751 Patent Claim Elements	Applicants' Claims Pending Before November 12, 1996
1	Contrast media for ultrasound imaging comprising gaseous microbubbles selected from the group consisting of hexafluoropropylene, octafluoropropane, octafluoro-2-butene, hexafluoro-2-butyne, hexafluorobuta-1,3-diene, octafluorocyclobutane and decafluorobutane.	• U.S.S.N. 08/456,385 (now U.S. Patent No. 5,685,551), 9/16/95 Amendment: 36. A suspension according to claim 36 [sic - 35], wherein said gas is a freon. 35. A microbubble suspension comprising gas microbubbles of a physiologically acceptable fluorine-containing entrappable gas. [Applicants' claim 36 includes substantially the same subject matter as '751 claim 1. As an initial matter, both claim 1 of the '751 patent and Applicants' claim require gas microbubbles of a physiologically acceptable freon. Indeed, although '751 claim 1 recites a group of specific freons, they are included in and not patentably distinct from the genus physiologically acceptable freon of Applicants' claims. Moreover, as Applicants' claims do not include any use limitations, they certainly encompass use as an ultrasound contrast agent. In any event, this limitation is not believed to be material to patentability. Therefore, claim 36 includes substantially the same subject matters '751 claim 1. However, Applicants contend that the claims' microbubbles are separately patentable over the '751 patent claims.] • U.S.S.N. 07/991,237 (now U.S. Patent No. 5,413,774), claims filed 12/16/92: 14. Suspensions of gas filled microvesicles distributed in an aqueous carrier liquid to be used as contrast agents in ultrasonic echography, characterized in that the gas is physiologically acceptable and such that at least a portion thereof has a solubility in water, expressed in liter of gas by liter of water under standard conditions, divided by the square root of the molecular weight does not exceed 0.003.

'751 Patent Claim	'751 Patent Claim Elements	Applicants' Claims Pending Before November 12, 1996
		[Applicants' claim 14 includes substantially the same subject matter as '751 claim 1. As an initial matter, both '751 claim 1 and Applicants' claim 14 require contrast media. Although Applicants' claim does not explicitly require microbubbles, they are included in the recited "microvesicles." Indeed, the specification of 07/991,237 defines microvesicles to include microbubbles as well as microballoons. (p. 1) See also dependent claim 16.[3] Therefore, both '751 claim 1 and Applicants' claim 14 include contrast media consisting of microbubbles. Moreover, although claim 1 requires specific fluorinated gases, they meet the gas criteria recited in Applicants' claim and thus are all encompassed by the claim. Indeed, several of these gases are recited in dependent claim 3.[4] Therefore, the gases recited in '751 claim 1 are included in and patentably indistinct from the gas genus of Applicants' claim. Therefore, Applicants' claim 14 encompasses substantially the same subject matter as '751 claim 1. However, Applicants contend that the claim's microvesicles are separately patentable over the '751 patent claims.] • U.S.S.N. 08/456,385 (now U.S. Patent No. 5,658,551), 4/18/95 Amendment 35. (Amended) A microbubble suspension comprising gas microbubbles of a physiologically acceptable, fluorine-containing entrappable gas or a mixture of a fluorine-containing entrappable gas with CO_2, nitrogen or H_2O in a suspension of dissolved or dispersed surfactants, at least one of the surfactants being a film-forming phospholipid present in the suspension at least partially in lamellar or laminar form.

[3] Claim 16 recites:

16. Aqueous suspensions according to claim 14, in which the microbubbles are microbubbles filled with said physiologically acceptable gas suspended in an aqueous carrier liquid containing phospholipids whose fatty acid residues contain 16 carbons or more.

[4] Claim 3 recites:

3. The method of claim 1, in which the physiologically acceptable gas used is selected from SF_6, SeF_6, Freon® such as CF_4, $CBrF_3$, C_4F_8, $CClF_3$, CCl_2F_2, C_2F_6, C_2ClF_5, $CBrClF_2$, $C_2Cl_2F_4$, CBr_2F_2 and C_4F_{10}.

'751 Patent Claim	'751 Patent Claim Elements	Applicants' Claims Pending Before November 12, 1996
		[Applicants' claim 35 includes substantially the same subject matter as '751 claim 1. As an initial matter, both claim 1 of the '751 patent and Applicants' claim 35 require microbubbles of a physiologically acceptable freon. Indeed, although '751 claim 1 recites a group of specific freons they are included in and patentably indistinct from the genus physiologically acceptable freon of Applicants' claims. Moreover, as Applicants' claim does not include any use limitations, it certainly encompasses use as an ultrasound contrast agent. In any case, this limitation is not believed to be material to patentability. Therefore, claim 35 includes substantially the same subject matter as '751 claim 1. However, Applicants contend that the claim's microbubbles, gas mixtures and surfactants are separately patentable over the '751 patent claims.] • U.S.S.N. 08/352,108, claims filed 11/30/94: 4. The ultrasound contrast medium of claim 3, wherein the fluorine-containing gas is sulfur hexafluoride or octafluorocyclobutane. 3. The ultrasound contrast medium of claim 2, wherein the fluorine-containing gas is selected from the group consisting of SF_6, CF_4, C_2F_6, C_2F_8, C_3F_6, C_3F_8, C_4F_6, C_4F_8, C_4F_{10}, C_5F_{10}, C_5F_{12} and mixtures thereof. 2. The ultrasound contrast medium of claim 1, wherein gas (B) is a fluorine-containing biocompatible gas. 1. An injectable ultrasound contrast medium comprising biocompatible at body temperature gaseous substances which when in suspension in an aqueous carrier liquid containing usual surfactants, additives and stabilizers provide contrast agents for ultrasound echography, characterized in that the medium is a mixture of gases (A) and (B) in which, at least one of the gases (B), present in an amount of between 0.5-41% by vol., has a molecular weight greater than 80 daltons and its solubility is water is below 0.0283 ml of gas per ml of water measured under standard conditions, the balance of the mixture being gas A.

'751 Patent Claim	'751 Patent Claim Elements	Applicants' Claims Pending Before November 12, 1996
		[Applicants' claims 3 and 4 include substantially the same subject matter as '751 claim 1. Both '751 claim 1 and Applicants' claims include contrast media for ultrasound imaging including the recited gases. Although Applicants' claims are not limited to microbubbles, the specification and claim 6 make clear that they encompass microbubbles.[5] Therefore, both '751 claim 1 and Applicants' claims encompass contrast media for ultrasound imaging comprising gaseous microbubbles selected from the recited group of gases and these claims encompass substantially the same subject matter. However, Applicants contend that the claims' "surfactants, additives and stabilizers," and its gas mixtures are separately patentable over the '751 patent claims.] • U.S.S.N. 08/380,588 (now U.S. Patent No. 5,578,292) 10/12/95 Amendment: 28. The contrast agent of claim 27, in which the Freon is selected from the group consisting of CF_4, $CBrF_3$, C_4F_8, $CClF_3$, CCl_2F_2, C_2F_6, C_2ClF_5, $CBrClF_5$, $CBrClF_2$, $C_2Cl_2F_4$, CBr_2F_2 and C_4F_{10}. 27. The contrast agent of claim 26 in which the halogenated hydrocarbon is selected from the group consisting of SF_6 and Freon(s). 26. A contrast agent for ultrasonic echography comprising gas-filled microvesicles suspended in a liquid carrier phase, the microvesicles being either microbubbles bonded [sic - bounded] by an evanescent gas/liquid interfacial closed surface of microballoons bounded by a material envelope, wherein the microvesicles contain a gas mixture of a first gas and a second gas, the second gas being a physiologically acceptable hydrocarbon.

[5] The specification of U.S.S.N. 08/352,108 explains "the invention relates to injectable ultrasound contrast medium in the form of microbubbles. . ." Similarly, original claim 6 recites:

6. An injectable ultrasound contrast agent comprising a suspension of gas filled microbubbles or microballoons in a physiologically acceptable aqueous carrier comprising usual surfactants, additives and stabilisers, characterized in that the gas is a gas mixture of at least two biocompatible gases A and B in which at least one gas (B) present in an amount of between 0.5-41% by vol. has a molecular weight greater than 80 daltons and solubility in water below 0.0283 ml per ml of water at standard conditions, the balance of the mixture being gas A.

'751 Patent Claim	'751 Patent Claim Elements	Applicants' Claims Pending Before November 12, 1996
		[Applicants' claim 28 includes substantially the same subject matter as '751 claim 1. Indeed, both '751 claim 1 and Applicants' claim include contrast media for ultrasound imaging comprising microbubbles of the recited gases. However, Applicants contend that the claims' microvesicles, microbubbles, microballoons and gas mixtures are separately patentable over the '751 patent claims.]

Exhibit 3
To Request For Interference

135(b) Showing For Quay '688 Patent

If Quay's new, broad definition of free gas microbubbles is adopted, the '688 patent claims may be construed to encompass surfactant stabilized microbubbles and thus to interfere with Applicants' claims. See footnote 2 in the Request For Interference filed herewith. The chart below assumes this interfering construction of the '688 patent claims and establishes that claims pending in Applicants' parent applications prior to April 25, 1996, the one year anniversary of the '688 patent issue date, encompass substantially the same subject matter as at least one '688 patent claim.

'688 Patent Claim	'688 Patent Claim Elements	Applicants' Claims Pending Before April 25, 1996
1	Biocompatible ultrasound contrast media comprising free gas microbubbles of a fluorine containing hydrocarbon.	• U.S.S.N. 08/456,385 (now U.S. Patent No. 5,658,551), 9/6/95 Amendment: 40. A suspension according to claim 35 wherein the suspension comprises dissolved or dispersed surfactants, at least one of the surfactants being a film-forming phospholipid present in the suspension at least partially in lamellar or laminar form. 35. A microbubble suspension comprising gas microbubbles of a physiologically acceptable fluorine-containing entrappable gas. [Assuming that Quay's new, broad construction of "free gas microbubbles" is adopted, Applicants' claim 40 encompasses substantially the same subject matter as '688 claim 1. As an initial matter, both '688 patent claim 1 and Applicants' claim 40 require surfactant stabilized microbubbles of a biocompatible fluorine-containing gas. While '688 claim 1 requires fluorine containing hydrocarbons, this limitation is included in and is not separately patentable over the genus "physiologically acceptable fluorine-containing entrappable gas" of Applicants' claims. Indeed, '688 patent claim 3 requires a fluorine-containing gas which is not a hydrocarbon (sulfur hexafluoride). Moreover, as Applicants claims do not include a use limitation they clearly encompass use as ultrasound contrast media. In any event, this limitation is not believed to be material to patentability. Thus, Applicants' claim 40 encompasses substantially the same subject matter as '688 patent claim 1. However, Applicants contend that the claim's microbubbles and surfactants are separately patentable over the '688 patent claims.]

'688 Patent Claim	'688 Patent Claim Elements	Applicants' Claims Pending Before April 25, 1996
		• U.S.S.N. 08/456,385 (now U.S. Patent No. 5,658,551), 4/18/96 Amendment: 35. (Amended) A microbubble suspension comprising gas microbubbles of a physiologically acceptable, fluorine-containing entrappable gas <u>or a mixture of a fluorine-containing entrappable gas with CO_2, nitrogen or H_2O in a suspension of dissolved or dispersed surfactants, at least one of the surfactants being a film-forming phospholipid present in the suspension at least partially in lamellar or laminar form</u>. [Assuming that Quay's new, broad construction of "free gas microbubbles" is adopted, Applicants' claim 35 encompasses substantially the same subject matter as '688 claim 1. As an initial matter, both '688 patent claim 1 and Applicants' claim 35 require surfactant stabilized microbubbles of a biocompatable fluorine-containing gas. While '688 claim 1 requires fluorine-containing hydrocarbons, this limitation is included in and is not separately patentable over the genus "physiologically acceptable, fluorine-containing entrappable gas" of Applicants claims. Indeed, '688 patent claim 3 requires a non-hydrocarbon fluorine-containing gas (SF_6). Moreover, as Applicants' claim does not include a use limitation, it clearly encompasses use as ultrasound contrast media. In any event, this limitation is not believed to be material to patentability. Thus, Applicants' claim 35 encompasses substantially the same patentable subject matter as '688 patent claim 1. However, Applicants contend that the claim's microbubbles, gas mixtures and surfactants are separately patentable over the '688 patent claims.] • U.S.S.N. 07/991,237 (now U.S. Patent No. 5,413,774), claims filed 12/16/92: 16. Aqueous suspensions according to claim 14, in which the microvesicles are microbubbles filled with said physiologically acceptable gas suspended in an aqueous carrier liquid containing phospholipids whose fatty acid residues contain 16 carbons or more. 14. Suspensions of gas filled microvesicles distributed in an aqueous carrier liquid to be used as contrast agents in ultrasonic echography, characterized in that the gas is physiologically acceptable and such that at least a portion thereof has a solubility in water, expressed in liter of gas by liter of water under standard conditions, divided by the square root of the molecular weight which does not exceed 0.003.

'688 Patent Claim	'688 Patent Claim Elements	Applicants' Claims Pending Before April 25, 1996
		[Assuming that Quay's new, broad construction of "free gas microbubbles" is adopted, Applicants' claim 16 encompasses substantially the same subject matter as '688 patent claim 1. As an initial matter, like '688 patent claim 1, Applicants' claim 16 includes a contrast agent comprising surfactant (e.g. phospholipid) stabilized microbubbles. Although '688 claim 1 requires a fluorine-containing hydrocarbon, these gases are included in and is not separately patentable over the genus defined by Applicants recited criteria. Indeed, the specification and dependent claim 3 establish that fluorine containing hydrocarbons are preferred gases.[1] Thus, claim 16 encompasses contrast agents which contain surfactant stabilized microbubbles of a fluorine-containing hydrocarbon. Consequently, it includes substantially the same subject matter as '688 claim 1. Applicants contend that the claim's microvesicles, microbubbles and phospholipids are separately patentable over the '688 patent claims.] • U.S.S.N. 08/352, 108, (now U.S. Patent No. 5,536,610) claims filed 11/30/94: 7. The ultrasound contrast agent of claim 6, wherein gas (B) is a fluorine-containing biocompatible gas. 6. An injectable ultrasound contrast agent comprising of [sic] a suspension of gas filled microbubbles or microballoons in a physiologically acceptable aqueous carrier comprising usual surfactants, additives and stabilizers, characterized in that the gas is a gas mixture of at least two biocompatible gasses A and B in which at least one gas (B) present in an amount of between 0.5 - 41% by vol. has a molecular weight greater than 80 daltons and solubility in water below 0.283 ml per ml of water as standard conditioner, the balance of the mixture being gas A.

[1] Claim 3 recites:

> 3. The method of claim 1, in which the physiologically acceptable gas used is selected from SF_6, SeF_6, Freon® such as CF_4, $CBrF_3$, C_4F_8, $CClF_3$, CCl_2F_2, C_2F_6, C_2ClF_5, $CBrClF_2$, $C_2Cl_2F_4$, CBr_2F_2 and C_4F_{10}.

Similarly, the specification of U.S.S.N. 07/991,237 explains that preferred gases "are, for instance, halogenated hydrocarbons like the freons and stable fluorinated chalcogenides like SF_6, SeF_6 and the like." (p. 11).

'688 Patent Claim	'688 Patent Claim Elements	Applicants' Claims Pending Before April 25, 1996
		8. The ultrasound contrast agent of claim 7, wherein the fluorine-containing gas is selected from the group consisting of SF_6, CF_4, C_2F_6, C_2F_8, C_3F_6, C_3F_6, C_3F_8 and C_4F_6, C_4F_8, C_4F_{10}, C_5F_{12} and mixtures thereof. [Assuming that Quay's construction of "free gas microbubbles" is adopted, Applicants claim 7 encompasses substantially the same subject matter as '688 claim 1. Both claim 7 and '688 claim 1 include biocompatible ultrasound contrast media comprising surfactant stabilized microbubbles of a fluorine-containing gas. Although '688 claim is limited to a fluorine containing hydrocarbon, this limitation is included in and patentably indistinct from the genus fluorine-containing gas of Applicants' claims. Indeed, Applicants' claim 8 makes clear that fluorine-containing hydrocarbons are preferred gasses. Therefore, Applicants' claim 7 encompasses substantially the same subject matter as '688 claim 1. However, Applicants contend that the claim's gas mixtures, microbubbles, microballoons, and "surfactants, additives and stabilizers" are separately patentable over the '688 patent claims.] • U.S.S.N. 08/380,588 (now U.S. Patent No. 5,578,292) 1/30/95 Prelim. Amendment: 25. An aqueous suspension comprising a dispersion of a contrast agent as claimed in claim 19 in a physiologically acceptable carrier liquid. 19. A contrast agent for echography in precursor form consisting of a dry powder comprising a lyophilized phospholipid and a stabilizer, said powder being dispersible in an aqueous liquid carrier to form an echogenic suspension of gas-filled microbubbles and stored under an atmosphere comprising a physiologically acceptable gas whose solubility in water, expressed in liter of gas by liter of water under standard conditions, divided by the square root of the molecular weight does not exceed 0.003.

'688 Patent Claim	'688 Patent Claim Elements	Applicants' Claims Pending Before April 25, 1996
		[Assuming that Quay's "free gas microbubble" limitation is interpreted to be directed to surfactant stabilized microbubbles, Applicants' claim 25 includes substantially the same subject matter as '688 patent claim 1. As an initial matter, like '688 patent claim 1, Applicants' claim 25 includes a contrast agent comprising surfactant stabilized microbubbles. Although claim 1 requires a fluorine-containing hydrocarbon, these gases are included and not separately patentable over the genus defined by Applicants' recited criteria. Indeed, the specification and dependent claim 22 establish that fluorine-containing hydrocarbons are preferred gases.[2] Therefore, Applicants' claim encompasses substantially the same subject matter as '688 claim 1, assuming that it is construed as discussed supra. Applicants contend that the claim's phospholipids and microbubbles are separately patentable over the '688 patent claims.] • U.S.S.N. 08/380,588 (now U.S. Patent No. 5,578,292) 10/12/95 Amendment: 28. The contrast agent of claim 27, in which the Freon is selected from the group consisting of CF_4, $CBrF_3$, C_4F_8, $CClF_3$, CCl_2F_2, C_2F_6, C_2ClF_5, $CBrClF_5$, $CBrClF_2$, $C_2Cl_2F_4$, CBr_2F_2 and C_4F_{10}. 27. The contrast agent of claim 26 in which the halogenated hydrocarbon is selected from the group consisting of SF_6 and Freon(s). 26. A contrast agent for ultrasonic echography comprising gas-filled microvesicles suspended in a liquid carrier phases, the microvesicles being either microbubbles bonded [sic - bounded] by an evanescent gas/liquid interfacial closed surface or microballoons bounded by a material envelope, wherein the microvesicles contain a gas mixture of a first gas and a second gas, the second gas being a physiologically acceptable halogenated hydrocarbon.

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2 The specification of U.S.S.N. 08/380,588 states that preferred gases include "stable fluorinated chalcogenides like SF_6, SeF_6 and the like." (p. 11) Claim 22 recites:

22. A contrast agent according to claim 19, in which the physiologically acceptable gas is selected from the group consisting of SF_6, SeF_6, CF_4, $CBrF_3$, C_4F_8, $CClF_3$, CCl_2F_2, C_2F_6, C_2ClF_5, CBrClF2, $C_2Cl_2F_4$, CBr_2F_2 and C_4F_{10}.

'688 Patent Claim	'688 Patent Claim Elements	Applicants' Claims Pending Before April 25, 1996
		30. The contrast agent of claim 26, in which the microvesicles are microbubbles bounded by an evanescent gas/liquid interfacial closed surface made from dissolved film-forming surfactants in lamellar or laminar form. [Assuming that Quay's "free gas microbubble" limitation is interpreted to be directed to surfactant-stabilized microbubbles, Applicants' claims 27 and 28 are directed to substantially the same subject matter as '688 claim 1. Like '688 claim 1, Applicants' claims require contrast media comprising microbubbles of a fluorine-containing gas. Although '688 claim 1 is limited to a fluorine-containing hydrocarbon, these gases are encompassed by and are patentably indistinct from the "halogenated hydrocarbon" or "SF_6 and Freon" genus of Applicants' claims. Indeed, claim 28 establishes that fluorine-containing hydrocarbons are preferred gases. Moreover, dependent claim 30 makes clear that Applicants' claims include surfactant stabilized microbubbles. Thus, Applicants' claims encompass substantially the same subject matter as '688 claim 1, assuming it is construed as discussed supra. However, Applicants contend that the claim's microvesicles, microbubbles, microballoons, surfactants and gas mixtures are separately patentable over the '688 patent claims.]